SESSION SUMMARY

Nontraditional Sites of Estrogen Action

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Many studies suggest that estrogen mimetic chemicals in the environment might be responsible for perturbations of sexual differentiation, sexual maturation, and adult reproductive proceses in both sexes. All estrogen target organs are at risk, including the external genitalia, gonads, reproductive tract, breasts, and the brain in both females and males. To appreciate how estrogens in the environment exert their effects, it is important to understand the different mechanisms by which estrogens act *in vivo*. Traditionally, the estrogenicity of a compound has been assumed to be a function of its binding affinity to the estrogen receptor. However, it is now becoming increasingly clear that endogenous estrogens act also via nongenomic mechanisms, raising the concern regarding our ability to adequately screen xenobiotics for reproductive toxicity.

Estrogen stimulation of a tissue results in a complex array of actions that occur over a 24- to 48-hour time span. The later estrogenic responses result from the regulation of gene expression by estrogen–receptor complexes. Other estrogenic effects, such as mitosis, appear to be mediated by peptide growth factors. In contrast, the mechanism by which the early estrogenic responses are regulated has remained an enigma since they occur too rapidly to be mediated by genomic mechanism.

Steroids and their mimetics exert a variety of effects that are observable seconds to minutes following stimulation of a susceptible tissue. Such effects include cation transport, glucose uptake, and water inhibition in the rat uterus and rapid changes in electrical activity in neurons and GH3 pituitary tumor cells. Plasma membrane-resident forms of steroid receptors have been proposed to mediate such actions.

C.S. Watson and colleagues describe a subpopulation of ERs residing in the plasma membrane of GH3 pituitary tumor cells, which mediate the rapid release of prolactin. The effect of estradiol is rapid and specific and takes place when ligand does not have access to the intracellular space. This system will be instrumental in understanding the role of nongenomic effects of estrogens in normal physiological and pathophysiological conditions. Moreover, the culture system developed by this group will be useful as a convenient screening test for nongenomic estrogenic actions.

The male reproductive system has not traditionally been thought of as a site of estrogen action, much less a source of estrogen synthesis. R.A. Hess and colleagues demonstrate the presence of aromatase in developing spermatids leading to the hypothesis that estrogen, synthesized by sperm, plays a role in the regulation of epididymal function. An understanding of the role of estrogen in the function of the epididymis may provide benefits in several areas, including the treatment of abnormalities in epididymal function, the potential development of a male contraceptive, and insight into the causes of epididymal lesions induced by neonatal exposure to estrogenic compounds such as DES. Moreover, the presence of estrogen-dependent processes in the male reproductive system renders these sites sensitive to the effects of xenobiotic estrogens in ways yet to be determined.

The importance of estrogens during early brain development is described by G.V. Callard in her presentation. During certain critical periods of early development, exposure to estrogens sets in motion processes that are revealed subsequently as male–female differences in brain structure or function. Endogenous estrogens can act in this regard either by genomic or nongenomic mechanisms. A nongenomic mechanism that is unique to the brain is exemplified by the catechol estrogens which have A-rings that resemble catecholamines and, as such, can either mimic or block the effects of natural estrogen as well as bind to catecholamine receptors. Aromatization of circulating androgens to estrogens in the brain provides an additional mechanism of organizational and activational effects of estrogen. Understanding an environmental chemical's ability to disrupt estrogen-dependent neural processes requires attention to all of the pathways. Using the goldfish brain as a model, Callard's group used the regenerative properties of the teleost central nervous system and visual system to study the effects of neuroestrogens on these processes as a preliminary step in studying xenobiotic actions.

The findings that were presented in this session challenge the receptor-mediated mechanism as the sole way in which estrogens act. As we delve into the complex actions of estrogen in animal and tissue culture models, it is becoming increasingly clear that not only are most tissues estrogen sensitive by virtue of the presence of specific gene-regulating receptors but that estrogens may regulate cellular function at alternative sites. These findings are important in explaining some of the actions of estrogens that occur too rapidly to be mediated by regulation of gene expression. Moreover, other molecules, which resemble estrogen in structure, may bind to these sites, resulting in unscheduled stimulation of specific processes leading to malfunction, disordered differentiation, and toxicity. Accordingly, estrogen receptor-binding per se is not a reliable predictor of an environmental chemical's ability to disrupt estrogen-dependent processes. The information that was presented in this session is fundamental to understanding the spectrum of the modes of estrogen *in vivo* and the potential for toxicity of estrogenic xenobiotics in the environment.

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